Gene Ownership versus Access: Meeting the Needs

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Two developments, which simultaneously and independently occurred in the 1980s, have substantially impacted the way drugs are currently being discovered and developed. First, there was a significant change in the technology employed for drug discovery. Traditionally, drugs were discovered using organs, tissues, cells or extracts thereof in screens to identify active pharmaceuticals. These traditional methodologies have been replaced by the use of technology involving specific molecular targets. These biotechnological targets may be receptors responsible for unique cell interactions associated with a disease or an enzyme that can catalyze a distinct biochemical reaction associated with a disease. The ability to identify and produce these unique proteins by recombinant techniques has resulted, in turn, in a wide range of mechanism-based screens. Of the 40 top selling drugs (worldwide sales 1993), 25 were identified by a specific mechanism of action: 13 were receptor agonists/antagonists; eight were enzymes/protease inhibitors; and four were channel blockers.

Second, the unencumbered availability of the materials and processes used in drug discovery has been noticeably decreasing. Prior to the rapid development of biotechnology, most pharmaceutical or chemical patents claimed active therapeutic agents, intermediates leading to active agents, processes of making active agents and intermediates, and methods of using active agents. The basic methodologies for chemical research were not generally patented. In 1980, Congress passed both the Stevenson-

Wydler Technology Innovation Act[1] and the Bayh-Dole Act[2] . Together, these Acts allowed government contractors, small businesses and nonprofit organizations to retain certain patent rights in government sponsored research and permitted the funded entity to transfer the technology to third parties. The original legislation was expanded in 1983 by Presidential Order[3] to include all government contractors. The 1980 legislation and subsequent amendments[4] (collectively termed Bayh-Dole) permit the contractor to grant exclusive licenses to government-funded contractor inventions. With the passage of the Federal Technology Transfer Act of 1986[5], Congress authorized federal laboratories to enter into cooperative research and development agreements (CRADAs) with private companies. The Act also required federal laboratories to agree in advance to assign or license to the collaborating party patents on inventions made by federal employees in the course of the collaborative research.

The stated intent of Bayh-Dole was to ensure that the patented results of federally funded research would be broadly and rapidly available for all scientific investigation, irrespective of the objectives of the research and the terms under which licenses are granted for the sale of products under the patents. Bayh-Dole effectively shifted federal policy from a position of putting the results of government-sponsored research directly into the public domain for use by all, to a pro-patent position that stressed the need for exclusive rights as an incentive for industry to undertake the costly investment necessary to bring new products to market. As a result, many of the basic materials and laboratory procedures that are universal to biotechnology and modern drug discovery have been the subject of patents and patent applications. As a result, accessibility is restricted.

The biotechnology materials and procedures that enhance drug discovery have been termed Research Tools. Research Tools are defined herein as biological or biochemical materials or processes that are useful for drug discovery and exclude materials or processes when used commercially. Examples of Research Tools include cDNA clones, receptors, monoclonal antibodies, transgenic animals and other inventions that can be used for drug discovery.

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[1]Pub. L. No. 96-480, 94 Stat. 2311 (1980) (codified as amended at 15 U.S.C. §§ 3701-3714).

[2]Pub. L. No. 96-517, § 6(a), 94 Stat. 3015, 3019-27 (1980) (codified as amended at 35 U.S.C. §§ 201-211).

[3]Presidential Memorandum to the Heads of Executive Departments and Agencies, Subject: government Patent Policy, 1983 Pub. Papers 248.

[4]Pub. L. No. 98-620, 98 Stat. 3335 [Trademark Clarification Act of 1984).

[5]Pub. L. No. 99-502, 100 Stat. 1785 (amending the Stevenson-Wydler Technology Innovation Act of 1980).

It is well recognized that one purpose of Bayh-Dole is to permit government funded patentees to grant exclusive licenses for the commercialization of products. This purpose can be accomplished while the broader intent of the Acts — that inventions be utilized as broadly as possible, is met. Accordingly, we believe that a federally funded patentee should grant non-exclusive licenses for Research Tools independent of licenses for products for sale. Further, we believe that the non-exclusive licenses should be available for reasonable fees. This broad access to Research Tools discovered under federally funded research programs by a non-exclusive license acts to foster competition among commercial laboratories to discover and ultimately develop novel human health products, thereby meeting the Congressional intent of Bayh-Dole. Because Merck supports a policy of licensing of patented inventions for research use separately from licensing for commercial development of products for sale, Merck Research Tool inventions are accessible for research purposes.

The current avalanche of genetic information from the Human Genome Project and other sequencing sources promises even greater advances for molecular medicine from Research Tools identified by these programs. With a complete, high resolution map of the human genome and an understanding of the genetic basis for disease, scientists should be able to create mechanism-based drugs that will result in improved therapies for known diseases and new therapies for diseases as yet unconquered. For this to happen in a timely manner, the basic Research Tools required for drug discovery must be readily available to the academic, governmental and industrial biomedical research community. Thus, availability will likely depend on ownership of genes and gene products and the methods of using those gene products.

Ownership of human genes first became a national and international issue when in 1992, the National Institutes of Health (NIH) filed patent applications claiming thousands of partial cDNA sequences which Craig Venter had termed expressed sequence tags (EST) (Adams et al. 1991). The NIH claimed the EST patent applications were filed to preserve a proprietary position for presumed valuable inventions (McGregor 1992). The NIH assumed that patent claims would issue with sufficient breadth to attract licensees that would develop products related to the partial genes. The NIH applications, however, created a worldwide controversy. American scientists associated with the human genome project strongly opposed the filing of EST patent applications because they believed the patents would have a negative impact on genome research (Roberts 1991). The science ministries of numerous European countries were very outspoken about how the patenting of genetic information would likely slow down the human genome project and change the economics of biomedical research. Due to the outcry from the worldwide scientific community and the inability to overcome the U.S. Patent and Trademark Office's (USPTO) rejection of the applications claims, the NIH simply did not respond to actions from the USPTO and the applications went abandoned.

The NIH applications raised questions about the patentability of human gene segments. The USPTO has issued patents claiming isolated and purified DNA (cDNA or genomic DNA) which encode a functional protein of known activity. Indeed, patents have been issued on short DNA fragments that are useful as diagnostics. The issuance of DNA patents requires that a compound (a gene, genomic sequence or cDNA sequence) must have been removed from its natural setting, be new, useful, unobvious and be enabled by the patent application.[6] An invention is considered novel if it has not been placed in the public domain, i.e., is not described in a publication or placed in commerce. The utility requirement can generally be met by demonstrating a particular use, such as a DNA sequence for gene therapy or as an intermediate for the manufacture of the encoded protein with an established function. A nonobvious invention is one that could not have been made with a reasonable expectation of success by a hypothetical person of "ordinary skill" in the relevant scientific field from publicly available information. Enablement requires that a patent application teach one skilled in the scientific area how to make and use the invention. In the case of the NIH partial sequences (EST) as discussed above, the USPTO maintained that the ESTs did not meet the utility requirement nor did the applications enable the inventions.

The Court of Appeals for the Federal Circuit (CAFC) has affirmed the validity of claims to full length cDNA or genomic DNA molecules, e.g., human erythropoietin and insulin like growth factor.[7] Indeed, obtaining a patent on a specific DNA molecule is quite beneficial in developing a patent portfolio around a specific protein therapeutic. In some instances, the protein may be known and not patentable and the only patent protection available will be for the isolated and purified DNA that can be used to make the protein therapeutic. This is important because large proteins may not be economically made by nonbiotechnological means. Product exclusivity through patent protection is required to offset the high research and development costs and the extended time to bring a product to market. The current estimate for this high risk enterprise is an average of 12 years from discovery to market and an investment of over $350 million.

With the lapse of the NIH EST patent applications the subject matter entered the public domain and was available to all researchers. The scientific community hoped that all genomic Research Tools would be readily available for biomedical research. Unfortunately, the privatization of EST research has thwarted this goal.

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[6]35 U.S.C. §§ 100-103 and 35 U.S.C. § 112.

[7]Amgen Inc. v. Chugai Pharmaceutical Co., 927 E 2d 1200,18 USPQ2d 1016 (Fed. Cir.), cert, denied, 502 U.S. 856 (1991) and In re Bell, 991E 2nd 781; 26 USPQ2d 1529 (Fed. Cir. 1993)

Several organizations are attempting to establish proprietary control over much of the sequence data on expressed human genes, including ESTs. Companies such as Human Genome Sciences (HGS) and Incyte are generating large EST data bases and are licensing access on an exclusive or non-exclusive basis to commercial entities (Dickson 1994a; Gen. Tech. News 1994). HGS initially maintained control over the utilization of the cDNA resources in their database and restricted access to collaborators, such as SmithKline Beecham, who were willing to invest significant sums of money for sequence information and rights to patented genes. Recently HGS has allowed academics limited access to the database but only if the institution agrees to allow HGS to develop any product identified by the use of the information gained from the database (Dickson 1994b). Unfortunately, this type of private ownership may prevent genomic scientists from pursuing full-length sequencing, mapping, and gene-based discoveries that would realize the goals to the Human Genome Project.

Merck has taken the view that the information represented by ESTs should be made broadly available with no commercial obligations. Indeed, access to the ESTs plus the corresponding physical cDNA clone will provide the key Research Tools that will speed the development of new biomedical knowledge. This knowledge should lead to new therapeutics for a wide range of diseases as the underlying pathophysiological mechanisms are better understood. The medical and commercial results of these efforts will benefit all interested parties, while providing opportunities and preserving incentives for investment in gene-based product development.

To this end, Merck has organized a collaborative effort termed the Merck Gene Index Project. This effort will make cDNA resources rapidly available to all scientists, for gene identification and mapping (Williamson and Elliston 1994). The Merck Gene Index will be a catalog of sequence data and identified clones arrayed from numerous cDNA libraries representing various organs and tissues and a variety of developmental stages. All scientists, whether public or private, will have full access to this standard set representing one clone per unique expressed gene. These clones will be characterized by single pass DNA sequencing and will be arrayed into microtitre plates and on filters as a publicly available resource. In cooperation with the IMAGE consortium (Integrated Molecular Analysis of Gene Expression), coordinated by Greg Lennon of Lawrence Livermore National Laboratory, a set of appropriate clones will be identified for sequencing by Robert Waterston, Richard Wilson, and their colleagues at the Genome Sequencing Center of the Washington University School of Medicine in St. Louis, Missouri. By identifying the repetitive and uniquely expressed genes, the number of clones that must be sequenced to capture all unique genes in a given sample should be reduced by an order of magnitude.

Washington University will generate sequence data from both the 5' and 3' ends of about 200,000 individual cDNA clones. The 3' end sequences will help facilitate mapping and full-length sequencing of specific cDNAs on human chromosomes, and facilitate the identification of a minimal set of unique gene cDNAs. The 5' end sequences will assist in identifying human cDNA sequence similarity to proteins of known function in existing databases. The new sequence data generated by Washington University will be submitted regularly via Database EST to Genbank (managed by the National Center for Biotechnology Information) where all interested researchers will have immediate and unrestricted access to the data, not only in the U.S., but also through Genbank's collaborative arrangements with its international partners, including the European Bioinformatics Institute, National Center for Genomic Resources and DNA Database of Japan. All users will be asked, though not required, to contribute results obtained using the Merck Gene Index data and/or clones to appropriate public databases.

The set of roughly 200,000 cDNA clones to be sequenced by Washington University will also be available from appropriate commercial and not-for-profit organizations, in the form of polymerase chain reaction (PCR) products gridded onto nylon membranes, and as individual clones and sets of clones in 384-well plates. These resources will then be distributed at reasonable cost via established networks to researchers who wish to do sequencing and mapping of individual genes or sets of genes, or for any research purpose.

This effort is anticipated to characterize between 50 percent and 85 percent of the unique expressed human genes, and to increase dramatically the amount and quality of publicly available sequence information on expressed genes. Scientists worldwide will have ready access to and be able to exploit particular clones as singletons or sets. The associated bioinformatics effort will ensure that the data generated are also captured in standardized fashion and made broadly available in public databases. These subsequent efforts using the Merck Gene Index as a research resource will likely lead to the identification of nearly 100 percent of expressed human genes.

The continued expansion of biomedical science and the discovery and development of unique highly specific therapeutics will depend on the availability of Research Tools to the academic, governmental and commercial research scientists. This can best be accomplished by having federally funded Research Tools available non-exclusively and by encouraging collaborations between commercial laboratories and academic and governmental laboratories to develop Research Tools, such as the Merck Gene Index. This broad access to Research Tools will advance science, accelerate the progress of medicine, and foster competition among commercial laboratories to discover and ultimately develop new human health products that will benefit all.

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